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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/516,310	03/01/2000	Yao-Zhong Lin	22000.0021U2	3622

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
11/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/516,310	LIN ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008 and 09 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,9-26 and 33* is/are pending in the application.

4a) Of the above claim(s) *16-26 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,10,11 and 13-15* is/are rejected.

7)☒ Claim(s) *9 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 6/9/08 has been entered.

Election/Restriction

Claims 16-26 and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/11/02.

Claim Amendments

Claims 34-40, and the status of said claims, are not present on the amendment filed 4/7/08. Any future amendments must list all of the claims which have been pending during prosecution of the instant application and their status. It is noted that Claims 34-40 have been previously canceled by applicant.

35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 10-11 and 13-15 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of importing a peptide, polypeptide or protein into a cell of a subject comprising administering to the subject a complex comprising the peptide, polypeptide or protein linked to a mammalian hydrophobic importation competent signal peptide comprising SEQ ID NO: 5, does not reasonably provide enablement for the method practiced with any mammalian hydrophobic importation competent signal peptide as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record in the previous Office Action (mailed 10/5/07) and for reasons outlined below.

Applicants traverse this rejection by asserting that applicants' discovery is that the hydrophobic portion of naturally occurring signal peptides possesses the structures that allow them to mediate importation into cells of attached proteins in the absence of special proteins and channels. Applicants assert that it would not represent undue experimentation for the skilled artisan to test hydrophobic regions from naturally occurring signal peptides that mediate translocation of proteins across the ER membrane for importation activity. With regard to the examiner's arguments regarding

the teachings of US 6,841,535, said arguments are moot given applicants amendment of the claims to delete the language reciting that the hydrophobic portion is "derived from" the hydrophobic portion of a naturally occurring signal peptide.

Applicant's arguments filed 8/9/08 and 4/7/08 have been fully considered but they are not persuasive. Not all hydrophobic portions from naturally occurring signal peptides that mediate translocation of proteins across the ER membrane can function as importation competent signal peptides. It is unclear what properties confer importation competence on a given hydrophobic portion from a given signal sequence. Essentially, the skilled artisan would need to practice trial and error experimentation in order to determine whether a given hydrophobic region is importation competent with regard to an attached peptide, polypeptide or protein with no guidance as to what particular naturally occurring signal peptide may or may not contain a hydrophobic portion which is importation competent for any given peptide, polypeptide or protein attached to it. This type of trial and error experimentation is the antithesis of enablement.

Essentially, applicants are arguing that the skilled artisan would be able **to identify** importation competent sequences by trial and error experimentation. However, the enablement requirement requires applicants to teach the skilled artisan how **to make** and use the claimed invention. Clearly, in the absence of trial and error experimentation, the instant disclosure does not provide an enabling disclosure sufficient to allow the skilled artisan to distinguish a importation competent hydrophobic portion sequence from a given signal peptide from a importation incompetent hydrophobic region sequence from another given signal peptide. The disclosure merely

provides an invitation for the skilled artisan to experiment to attempt to identify other hydrophobic portions which are importation competent.

Claims 6, 10-11 and 13-15 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below.

Applicants traverse this rejection by asserting that the claims are drawn only to methods of importing peptides, polypeptides or proteins using hydrophobic portions of a signal peptide of a protein which is secreted from cells. Applicants restate that the novel aspect of the invention involves the ability of the hydrophobic portion of a naturally occurring signal peptide to facilitate the signal peptide's ability to cross the cell membrane and that the hydrophobic portion of any signal peptide of a protein secreted from cells would have the ability to cross the plasma membrane. Applicants assert that the citation of the 6,841,535 patent or the V5 epitope tag by the previous examiner is not on point because the hydrophobic peptides disclosed in the '535 patent are not drawn from signal sequences which have already been shown to be capable of crossing cell membranes. Applicants assert that the properties of the hydrophobic region of the importation signal peptide that allow it to cross the ER membranes are the same

properties that allow it to cross the plasma membrane and that the examiner has not presented any reasoning or evidence to dispute this. Applicants assert that the invention does not represent new or unknown biological materials and that the skilled artisan could readily identify the hydrophobic region of any given naturally occurring signal peptide.

Applicant's arguments filed 2/12/08 have been fully considered but they are not persuasive. Applicants have provided no evidence that any hydrophobic region from any signal peptide is importation competent with regard to a biological material attached to said peptide. As noted in the previous Office Action, the art indicates that the mere presence of a hydrophobic region from a known signal peptide does not itself render the hydrophobic region importation active. The skilled artisan must empirically test any given hydrophobic region from any given signal peptide to determine whether it is importation competent. Applicants have not provided any structure – function relationship which would allow the skilled artisan to distinguish an importation competent hydrophobic region from a given signal peptide from an importation incompetent hydrophobic region from another signal peptide.

An examination of the art (pre and post-filing) provides no evidence that hydrophobic regions from all or the majority of signal peptides are importation competent. Indeed, even years after the effective filing date of the instant invention; the mechanisms by which certain peptides traverse biological membranes so as to import or deliver biologically active compounds into cells remain unclear (see Veach et al., previously cited by the examiner and Schwarze et al., TiPS, 2000. Vol. 21, pp. 45-48).

As noted by Schwarze et al., protein transduction domains possess basic amino acids such as Arg and Lys and Gros et al. (Biochim. Biophys. Acta, 2006, Vol. 1758, pp. 384-393) teaches that a protein transduction domain (Pep-1) possesses hydrophobic tryptophan rich motifs **and hydrophilic domains** which are necessary for importation of cargoes across the cell plasma membrane. However, no references teach that the mere presence of a hydrophobic region from a signal peptide has protein transduction activity. The art appears to teach that the ability of a peptide to function as an importation peptide must be determined empirically since it is unclear how these peptides function to effect transduction of biological materials into cells.

Contrary to the fact pattern in *Amgen*, the importation competent peptides used in the claimed method are described by what they do rather than what they are. A description of what a material does rather than what it is, is generally insufficient to meet the written description requirement of 112, 1st paragraph. The recited importation peptides represent portions of known signal peptides, but applicants have not directed the skilled artisan to what specific signal peptides comprise hydrophobic portions that possess the claimed activity. Without a disclosure of which hydrophobic portions of which signal peptides have the desired importation function, the claimed methods cannot be said to be described. An adequate description of the claimed peptides requires a precise definition, such as by structure, formula or physical properties, not a mere wish or plan for obtaining the claimed chemical invention by screening hydrophobic regions from known signal peptides.

In summary, applicants have not demonstrated, and the art has not disclosed, a structure – function relationship between hydrophobic regions of signal peptides and the capacity of these hydrophobic regions to transduce (import) biological materials across cell membranes and into cells. An examination of the art indicates that the ability of a given hydrophobic sequence of amino acids to function as a protein transduction domain is unpredictable and would need to be determined empirically. The skilled artisan would therefore not conclude that applicants were in possession of the claimed genus of importation peptides used in the claimed methods.

No Claims are allowed.

Claims 9 and 12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Low, Ph.D., can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 5, 2008

/David Guzo/
Primary Examiner
Art Unit 1636